

# Lymph Node and Perinodal Tissue Tumor Involvement in Patients With Esophagectomy and Three-field Lymphadenectomy for Carcinoma of the Esophagus

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**Background:** Lymph node metastasis is a definitive prognostic factor; however, perinodal fat tumor invasion has not been fully elucidated.

**Methods:** Periesophageal nodes and the surrounding fibrofatty tissue obtained from 131 patients who underwent esophagectomy were examined.

**Results:** Of 9,789 nodes removed, 645 (6.6%) demonstrated invasion and 143 (1.5%) showed perinodal involvement. Of 131 patients, 97 (74.0%) had lymph node involvement and 43 (32.8%) had perinodal fat involvement. The incidence of perinodal tissue involvement correlated significantly with the number of nodes involved; 23 (42.6%) of 54 patients with a total of 1–8 nodes involved and 19 (95.0%) of 20 patients with 9 or more involved nodes had perinodal involvement. The 5-year survival for 33 patients without involved nodes or perinodal tissue extension was 59.7%, compared to 14.0% for 43 patients with perinodal fat involvement.

**Conclusion:** Perinodal tissue carcinoma into the periesophageal fibrofatty tissue was a decisive prognostic factor in patients with curative resection for esophageal carcinoma. *J. Surg. Oncol.* 64:12–16 © 1997 Wiley-Liss, Inc.

**KEY WORDS:** esophageal carcinoma; three-field lymphadenectomy; lymph node metastasis; perinodal tissue cancer involvement

## INTRODUCTION

Esophageal carcinoma with primary tumor invasion of the submucosa frequently metastasizes to the lymph nodes [1]. The degree of involvement of lymph nodes, particularly the number of nodes with metastases, has been found to be a definitive prognostic factor. Skinner et al. [2] have considered the critical number of involved nodes to be three or four. Some investigators, however, regard tumor spread to the mediastinum, regardless of the number of involved nodes, as an indication of widespread systemic disease [3]. In addition, Gatzinsky et al. [4] has reported that at least half of patients with lymph node metastases have had extension of carcinoma into perinodal tissues. Some correlation between the number of involved nodes and the presence of perinodal fat extension of carcinoma may exist. The aim of this article is to determine the relationship between node involvement

and perinodal fat involvement and to differentiate patients with curable node involvement from those with more systemic lymphatic spread.

## MATERIALS AND METHODS

We evaluated 131 patients with squamous cell carcinoma of the thoracic esophagus who underwent resection with simultaneous three-field lymphadenectomy from 1983 to 1992. Eligibility criteria for the three-field lymphadenectomy and esophagectomy have been described previously [5]. Surgical specimens were examined histologically using hematoxylin-eosin staining and classi-

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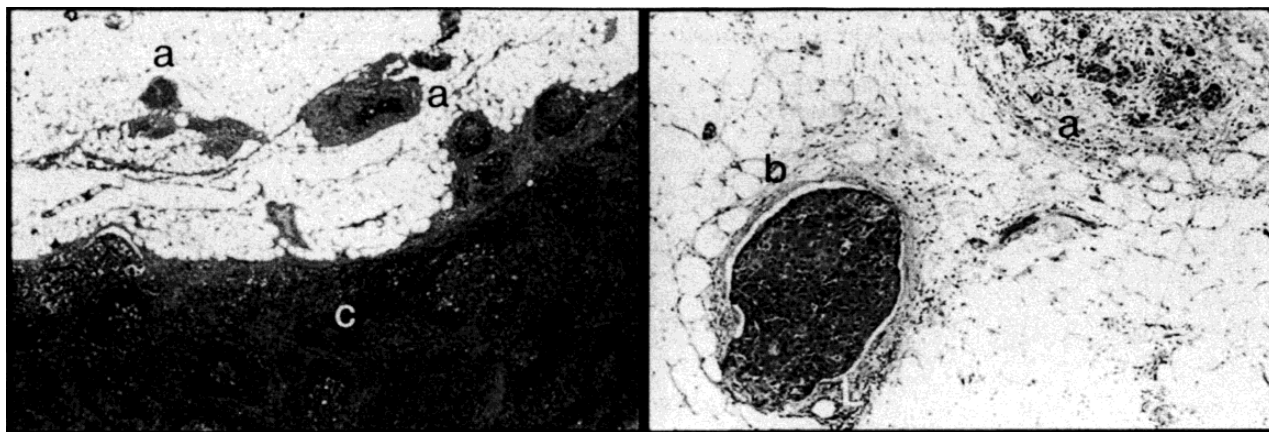


Fig. 1. Histologic specimen demonstrating perinodal fat invasion. Perinodal cancer invasion is seen in the fibrofatty tissue (a), and in lymphatics and blood vessels (b) surrounding the lymph node (c).

fied according to the TNM system [6]. All patients underwent RO esophagectomy with curative intent. In order to assess the extent of node involvement and perinodal tumor growth, both the nodes and the surrounding fibrofatty tissue were sectioned. The area predominantly sectioned included the lymph node hilus. If cancer cells were present in lymph nodes or in fibrofatty tissue surrounding nodes, the specimen was designated as having node involvement (NI) or perinodal tissue involvement (PI), respectively (Fig. 1). Nodes were classified by location as neck, upper, middle, and lower mediastinum, and abdominal nodes. This classification was consistent with previous reports [5,7] in which the recurrent nerve node chains [8] were classified by their location in the neck or the upper mediastinum. The abdominal nodes were classified further as upper gastric and retroperitoneal nodes; the former included paracardiac nodes and nodes along the left gastric artery, and the latter included celiac axis, splenic artery, and common hepatic artery nodes. Follow-up evaluation was possible for at least 31 months in the 131 patients with the exception of four patients (3.1%) who died within 30 days after surgery. In this follow-up evaluation, ultrasonography and computed tomography were performed every 3–6 months. Survival rates were determined using the Kaplan-Meier method, and the differences were evaluated by the generalized Wilcoxon test. Chi-square tests for categorical variables were used. A *P* value of <0.05 was considered significant.

## RESULTS

### Clinical and Pathologic Characteristics of Patients With and Without Perinodal Tissue Involvement

The average age of the patients was  $60.3 \pm 8.1$  years. Of 22 T1 tumors, 20 demonstrated submucosal invasion. Fifty-four stage IV patients had no evidence of blood-

borne metastases at the time of operation, but evidence of distant lymphatic metastasis was found. The PI correlated significantly with TNM p-N classification, NI, and total number of nodes involved ( $P < 0.0001$ , Table I). Of the 54 patients with a total of 1–8 nodes involved, 23 (42.6%) had perinodal fat involvement, as opposed to 19 (95.0%) of the 20 patients with more than 9 involved nodes.

### Incidence of Involvement of Lymph Nodes and Perinodal Fat

A total of 9,789 nodes with their surrounding fibrofatty tissue was removed and examined, with a mean of  $74.7 \pm 20.1$  nodes per patient (Table II). The percent of NI in the lymph node chains along the recurrent nerve, including the paraesophageal nodes in the neck and/or upper mediastinum, was 9.5% (185/1945), which was almost identical to that of the abdominal nodes (9.3%). The supraclavicular nodes were less frequently involved, with an incidence of 2.3%. The incidence of PI was <2.5% for all respective anatomic sites, although perinodal fat tumor extension was seen in all regions from the neck to the abdomen.

### Incidence and Location of Lymph Node and Perinodal Tissue Involvement in 131 Patients

Ninety-seven (74.0%) patients had NI and 43 (32.8%) patients had PI (Table III). Of the 53 patients who had a total of 1–4 involved nodes, the region most frequently involved by tumor was the upper gastric region, followed by the upper mediastinum. The most frequent site for PI was also the upper gastric region, again, followed by the upper mediastinum. Of 9 patients who had 1–4 involved nodes, PI occurred from the cervical paraesophageal to the upper gastric regions. The number of nodes involved is compared to the percent of removed nodes that were

**TABLE I. Clinical and Pathologic Characteristics of 131 Patients With Carcinoma of the Esophagus With and Without Perinodal Tissue Involvement**

Characteristic	Category	No. of patients		P Value ( $\chi^2$ test)
		With PI	Without PI	
Sex	Male	42	83	0.6761
	Female	1	5	
Age (years)	37–60	21	43	0.7059
	61–70	19	35	
	71–75	3	10	
Tumor length(cm)	1.0–5.0	10	36	0.1080
	5.1–7.0	14	26	
	7.1–20.0	19	26	
Tumor location	Upper	3	12	0.2079
	Middle	29	55	
	Lower	11	12	
Tumor histology				
well differentiated		16	38	0.7895
moderately differentiated		19	34	
poorly differentiated		8	16	
Vessel invasion <sup>a</sup>	Absent	5	30	0.0118
	Present	38	58	
p-T	T1	4	18	0.2811
	T2	7	19	
	T3	31	49	
	T4	1	2	
p-N	NO	2 <sup>b</sup>	39 <sup>c</sup>	<0.0001
	N1	41	49	
Tumor stage	I	0	10	0.0004
	II	6	30	
	III	9	22	
	IV	28	26	
NI	Absent	1 <sup>d</sup>	33	<0.0001
	Present	42	55	
Total no. of NI	0	1 <sup>d</sup>	33	<0.0001
	1–4	9	44	
	5–8	14	10	
	9–51	19	1	

<sup>a</sup>Including lymphatic, venous, or perineural invasion. <sup>b</sup>One of the two patients had not only a single involved node, but also a single node with PI in the cervical paraesophageal region, with classification as p-NO or stage IV based on TNM classification. <sup>c</sup>Six of the 39 patients had single involved nodes with no PI. <sup>d</sup>Only one patient had PI in the upper gastric region without NI elsewhere. NI = node involvement; PI = perinodal involvement.

involved (Table IV) [9]. None of the 77 patients with 1–8 involved nodes had more than 20% of removed nodes involved ( $P < 0.0001$ ).

### Tumor Recurrence

The incidence of tumor recurrence was lower in patients without NI or PI, compared to patients with NI or PI (Table V). The most frequent site for recurrence was the upper mediastinum in patients without NI or PI, whereas blood-borne metastases and dissemination occurred more frequently in patients with NI or PI.

**TABLE II. Cancer of the Esophagus: Incidence of Node and Perinodal Involvement in the 9,789 Nodes Removed**

Sample site	No. of removed nodes	No. (%) of nodes with NI	No. (%) of nodes with PI
Neck			
Supraclavicular	2,870	67 (2.3)	11 (0.3)
Paraesophageal <sup>a</sup>	569	49 (8.6)	7 (1.2)
Mediastinum			
Upper	2,002 <sup>b</sup>	163 (8.1) <sup>c</sup>	34 (1.7) <sup>d</sup>
Middle	1,117	76 (6.8)	20 (1.8)
Lower	520	43 (8.2)	6 (1.1)
Abdomen			
Upper gastric	2,196	204 (9.3)	52 (2.4)
Retroperitoneal	515	45 (8.7)	13 (2.5)
Total no. of samplings	9,789	645 (6.6)	143 (1.5)

<sup>a</sup>Includes bilateral recurrent nerve lymph nodes in the neck. <sup>b,c,d</sup>1,376 (68.7%) of the 2,002<sup>b</sup>, 136 (83.4%) of the 163,<sup>c</sup> or 33 (97.1%) of the 34 nodes<sup>d</sup> were adjacent to the recurrent nerves, respectively. NI = node involvement; PI = perinodal involvement.

**TABLE III. Incidence and Location of Lymph Node and Perinodal Involvement in 131 Patients With Cancer of the Esophagus**

Sample site	No. (%) of patients with NI $\leq$ 4 NI <sup>a</sup>		No. (%) of patients with PI $\leq$ 4 NI <sup>b</sup>	
Neck				
Supraclavicular	24 (18.3)	7	9 (6.9)	0
Paraesophageal	27 (20.6)	12	7 (5.3)	2
Mediastinum				
Upper	53 (40.5) <sup>c</sup>	19 <sup>c</sup>	16 (12.2) <sup>c</sup>	2 <sup>c</sup>
Middle	36 (27.5)	9	12 (9.2)	3
Lower	23 (17.6)	7	4 (3.1)	1
Abdomen				
Uppergastric	60 (45.8)	25	26 (19.8)	7
Retroperitoneal	14 (10.7)	3	6 (4.6)	0
Total no. of patients	97 (74.0)	53 (47.3)	43 (32.8)	9 (6.9)

<sup>a</sup>Patients with a total of 1–4 nodes involved. <sup>b</sup>Patients with PI but with a total of 1–4 NI. <sup>c</sup>Recurrent nerve lymph node chains and/or paraesophageal nodes in the upper mediastinum were involved in all patients. NI = node involvement, PI = perinodal involvement.

**TABLE IV. Cancer of the Esophagus: Number and Percent of Resected Nodes Involved in 97 Patients With Node Involvement**

No. of NI <sup>b</sup>	No. of NI/removed nodes <sup>a</sup>	
	1–19%	20–49%
1–4	53	0
5–8	24	0
9–51	10	10
Total no. of patients	87	10

<sup>a</sup>(No. of NI)/(No. of removed nodes)  $\times$  100 per patient. <sup>b</sup>Number of nodes involved per patient. NI = nodes involved.

TABLE V. Tumor Recurrence After Esophagectomy in 131 Patients

Site of recurrence	Without NI/PI 33 patients	With NI/without PI 55 patients	With PI 43 patients
Upper mediastinum, including the cervicothoracic region	5	7	9
Middle/lower mediastinum	1	2	1
Abdominal paraortic	2	4	5
Lung		7	8
Liver/bone/other	1	9	7
Dissemination	1	3	5
Anastomotic site	1	1	
Total no. of patients with recurrence;	8/33(24.2%)	29/55(52.7%)	28/43(65.1%)

NI = node involvement; PI = perinodal involvement.

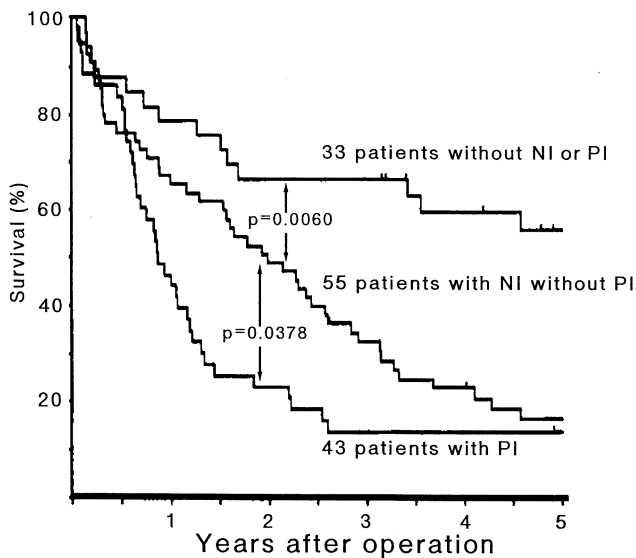


Fig. 2. Survival curves of patients according to lymph node or perinodal tissue involvement. The 2- and 5-year survival rates were, respectively, 66.7% and 59.7% for patients without NI or PI, 49.1% and 23.0% for patients with NI without PI, and 23.3% and 14.0% for patients with PI. NI = node involvement; PI = perinodal involvement.

### Survival

The overall survival rates were 62.6% at 1 yr, 45.1% at 2 years, 35.1% at 3 years, 29.4% at 4 years, and 25.8% at 5 years. Statistically significant difference in survival existed between patients without NI or PI and patients with NI without PI. In addition, survival rates were significantly lower in patients with PI compared to patients with NI without PI (Fig. 2).

### DISCUSSION

Few reports have presented a detailed analysis of surgically removed lymph nodes. Siewert and Rodes [9] examined an average of 42.7 nodes per patient undergoing esophagectomy with en bloc two-field lymphadenectomy. They found a positive correlation between the percent of removed nodes involved and prognosis, i.e., im-

proved prognosis was associated with <20% of removed nodes involved. In addition, when more than seven mediastinal nodes were involved, this factor acted as an independent prognostic factor associated with a worse outcome [9]. In this series, in which an average of 74.7 nodes were examined per patient, none of the patients with less than eight involved nodes had >20% of resected nodes involved, suggesting a relatively low incidence of perinodal tissue involvement. In contrast, all but one of the 20 patients with nine or more involved nodes had perinodal involvement, which was associated with a high incidence of tumor recurrence and an unfavorable outcome. Matsubara et al. [10] has analyzed 171 patients who underwent systematic dissection of regional nodes, including cervical nodes, and has reported that outcomes were unfavorable when more than seven nodes were involved. Therefore, when more than seven or eight nodes are involved, surgical cure of nodal metastases appears to be unlikely. The number of involved nodes appears to correlate with systemic lymphatic tumor spread when it exceeds nine.

Watanabe et al. [11] has demonstrated that perinodal infiltration of tumor into periesophageal fibrofatty tissue is a crucial prognostic factor. The incidence of perinodal infiltration increases with increasing depth of invasion of the primary tumor, as has been reported by Gatzinsky et al. [4]. The incidence of perinodal tissue involvement also correlates significantly with the number of involved nodes; 42.6% of the 54 patients with 1–8 nodes involved had perinodal fat involvement. Perinodal tissue invasion occurred most frequently in the upper gastric region and in the fibrofatty tissue adjacent to the lymph nodes along the recurrent nerve. In addition, perinodal tissue involvement appeared to extend along the course of the esophagus, even in patients with no more than four involved nodes. Matsubara et al. [10] have observed that the outcome in patients with lymph node involvement limited to the upper gastric region has been almost identical to that in patients without node involvement. Our previous report has revealed that recurrent nerve node metastasis is

a significant negative risk factor [5]. Anatomically, the upper gastric nodes lie in the gastropancreatic fold where en bloc lymphadenectomy is possible. However, no lymph node containing mesoesophagus exists in the upper mediastinum, as has been reported by Skinner [12]. This may be the reason that carcinoma recurs so frequently in the upper mediastinal region, and positive nodes in this region are associated with a worse prognosis [5,10]. Sarrazin and Voog [13] have theorized the existence of tracheal, visceral, and vascular fascial sheaths in the mediastinum; the recurrent nerve lymph node chains may lie between a tracheal and visceral sheath. The vascular sheath covers aorta and azygos vein and comprises the outermost fibrous layer posterior to the mediastinal pleura. This anatomic concept may provide a clear margin for resection of perinodal carcinoma if a surgeon can clear the lymph nodes and the vascular sheath, which has continuity with the mediastinal pleura and deep cervical fascia as well. Consequently, not only the number of lymph nodes with metastases, but also the perinodal tissue carcinoma extending into the peri-esophageal fibrofatty tissue was a decisive prognostic factor in patients who had curative resection for carcinoma of the thoracic esophagus.

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